Schechter, Alan 2018

Dr. Alan Schechter Oral History 2018

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Dr. Margolin: This is Dr. Gordon Margolin, volunteer in the Office of the NIH History in the Stetten Museum serving as a moderator today for this updated oral history with Dr. Alan Schechter. We are recording this session in the NIH Library's Audiovisual Facility on March 13, 2018.

Dr. Schechter who's currently the Chief of the Molecular Medicine Branch of NIDDK here at NIH started at this facility in 1965. We will be discussing as many activities, interests and accomplishments during this session. On three separate occasions, however, he has participated in recorded interviews, in 1998 when he reported about his childhood, schooling, training and early research endeavors, in 2001 when he elaborated on thoughts of the NIH and the changes he had noted over the years, and in 2003, when he reviewed his research endeavors up to that time, including protein chemistry with Dr. Anfinsen, hemoglobinopathies with focus of sickle cell disease and interest in Genetics and Immunology as applied to hemoglobin.

Since all of this information is available and already preprinted, we have chosen to repeat only a little bit of that, which segues into his more recent work, and to utilize this session to update these earlier oral presentations.

Dr. Schechter, welcome. We so much appreciate your time and your effort in this endeavor. Let's start by talking about your direction and accomplishments of your research over the last 20, 30, or whatever number of years. You can tell me in whatever order you'd like to talk about.

Dr. Schechter: Thank you, Dr. Margolin. I think for consistency let me begin at the beginning when I first came to NIH, and then quickly develop the story until the present.

In 1964 when I was a Resident, I basically had to choose between my research areas of molecular biology and protein chemistry with respect to the laboratory I wished to work in at the NIH. I covered this in some detail in previous interviews, but largely because of Dr. Nansen's personality, which I was aware of in interviews with him and through conversation with others, I chose to work in his laboratory rather than several others, which were comparable quality.

I opted for my research career to follow the track of protein chemistry rather than perhaps what later became known as molecular biology, and that had certain advantages and certain disadvantages in retrospect. I came to NIH on July 1, 1965, and I began to work with Dr. Charles Epstein who later became a prominent geneticist at the University of California in San Francisco. Dr. Epstein had just become an independent investigator within Dr. Nansen's larger laboratory, and I opted to work on several projects related to protein chemistry as I mentioned rather than some more genetic or cell biology projects, which were offered to me as a possible realm of investigation.

In the same, as I note, when I came to the laboratory, I was offered a choice of what I wanted to work with. I wasn't assigned to work on something specific, and I think this was an important aspect of the training in that laboratory, which was called the Laboratory of Chemical Biology that I saw from the very beginning.

Dr. Margolin: Was that a typical approach at NIH to offer the young people their own options?

Dr. Schechter: I think probably not, and that was probably one of the very good aspects of that particular lab and a few other laboratories, and I think that [inaudible 00:04:34] my own approach to mentoring since then. I think it's an important issue in how things are done in mentoring and developing new scientists and new physician investigators.

Dr. Margolin: We're going to let you comment more on that later. So, [crosstalk 00:04:55]. That's fine. Thank you.

Dr. Schechter: I'd be delighted to. The other aspect of the choice made in that July 1965 was basically giving me a few papers and some reference books and saying, "Read up on it, and read up on the subject that you want to work on, and then figure out what experiments to do."

This, again, has advantages and disadvantages. One of the ironies was that in September of that year, 1965, one of my colleagues would come in the same day, published a paper in journal called "Biochemical Biophysical Research Communications", which was less than three months after we had both come. For me this was disheartening because at that point I hadn't even figured out then what my research questions were, or what my goals were.

So, actually I have to say that the first year went very slowly as I tried to formulate questions and to learn how to answer them. This was a tradition in that laboratory, which I think was an important one.

Dr. Margolin: Yes, as I recall, you were not a trained researcher when you came here. You were taken on, and let go on sort of a free line basis.

Dr. Schechter: Well, I differ that slightly. I mean I did not have formal Ph.D training, but I had worked in college in a laboratory, and eventually published a paper from that work, and in medical school I took advantage of several electives to pursue research projects, and I was an author of several more papers that did occur during that time, one of which with Dr. Bernard Weinstein in the procedure at National Academy of Sciences was the first evidence for the universality of the genetic code that Dr. Nirenberg had reported on here at NIH.

That paper for a while was extensively cited. So, I did have more research experience than most of the physicians coming to NIH at that point. But going back to the story of my work in the Laboratory of Chemical Biology, the problem I chose to work on was the effective heme on the folding of apomyoglobin, and I devoted most of my first two years to that project, later realizing that most of the questions I was trying to study were not meaningful because the heme and it's solution aggregated and it was very difficult to do quantitative analyses of measuring the binding of an aggregate to a protein.

But despite that, I was able eventually to publish one long paper in the "Journal of Molecular Biology", which at that point was a very important communication means in my field, which covered both classical molecular biology, and the type of protein chemistry that I was doing. I worked on several smaller projects, which also led to publications, but at the end of two years I thought of going back to medicine and training in Hematology. I was offered a position at the Albert Einstein Medical College where I trained, and I looked at that position, but felt that I needed more research training, and so then I then asked Dr. Anfinsen whether I could stay for some further time, and he said, "Sure".

My wife had to encourage me to ask. I always felt that if people wanted me, they would ask me, that I shouldn't ask them. But anyway, I found an external NIH fellowship and stayed in the laboratory for several more years. Dr. Epstein in the meantime had left NIH to go to the University of California, and therefore, I began to work directly with Dr. Anfinsen continuing the project that I had been working on as well as segueing into some more projects directly with him on the reforming of Staphylococcal nuclei and related proteins.

Gradually this work led to several papers, which were part of the work that was cited in Dr. Anfinsen's Nobel Prize citation by the Academy of Sciences in Sweden. I continued in this reign until about a year after Dr. Nansen's Nobel Prize when I came to realize that I had to find my own fuel of inquiry, that I could not continue to work directly with Dr. Anfinsen on his projects.

Dr. Margolin: But was your name cited in the Nobel Prize publication?

Dr. Schechter: Yes, it was. In fact, I wrote on behalf of Dr. Shannon the nomination letter for Dr. Nansen's Nobel Prize, and many of the words in my nomination letter were cited by the Nobel Committee. On the other hand, when Dr. Anfinsen went to Sweden to receive it in the paper that he published in "Science Magazine" afterwards, he cited to a large extent the work that he and I and a few other people, David Sachs, in particular were doing at that moment on the refolding of proteins as measured by homological techniques.

I was a little uncomfortable then because we had not published those results. I was not 100% sure they were all valid, but Dr. Anfinsen always felt that he should talk about the current work rather that what had done before. I think, fortunately, and virtually all of the work turned out to be valid and was later published in appropriate journals, but in preparing his Nobel lecture, he made use of much of our work, which was then still developing.

Dr. Margolin: I can imagine that made you feel a little bit uncomfortable at that time.

Dr. Schechter: Yes, it did. That was one of several ways in which I recognize that the position I had, which was sort of equivalent to what later became a staff scientist position, although it was not so-called then, which continued for the four or five years that I worked directly with Dr. Anfinsen, I had certain responsibilities.

Another one that I realized was that when we submitted a paper together, very often because his name was on it, the referring was somewhat superficial, which is very different from the situation now, when referring is almost always adversarial. But I realized then that we had greater responsibility in making sure everything was correct, and having various people read the manuscripts to try to ensure their reliability because the referring did not, or the editing did not always do that as rigorously as it might be for somebody less well known, the irony of the situation.

Dr. Margolin: It's a fairly normal human response, I would think, to treat a person like Dr. Anfinsen differently than other people.

Dr. Schechter: Yes. It has advantages and disadvantages. I think science has changed, and that sort of halo effect is less evident now than it was forty or fifty years ago.

Dr. Margolin: Yes, I think that will also come out in our later discussion about some of your activities outside of the direct science work when we talk further later on.

Dr. Schechter: Yes. But then again, as I mentioned in 1973, I felt the need to more fully divide an independent research program. Unfortunately, Dr. Anfinsen was offered no resistance or pushback to that, which probably did not occur in all such situations or all laboratories. I initially chose to work on transfer RNA and its interactions with the enzymes in protein biosynthesis, which caused the interaction between tRNA and the appropriate immuno acids. I chose to work on that because I wanted to work on nucleic acid protein interactions, again being aware of the beginning of what's nucleic acid chemistry at that moment.

One of the ironies was that Dr. Nansen's group was focused on staphylococcal nuclease, which destroys RNA easily, and I was trying to purify tRNA, which was very difficult to purify and was very little mass, and there were huge amounts of staphylococcal nuclease on all of the glassware and all the instruments in the laboratory. So the yields of our purification procedures were very, very poor, and after two years of work in this area, which I got one or two publications by doing a short sabbatical in Naples, Italy with a group that had previously worked in the Laboratory of Chemical Biology, but was now in Naples who were also studying the tRNA synthesis. I was able to get some results in Naples, but quickly back at NIH I found this too difficult to do in the laboratory focused on a nuclease.

Dr. Margolin: Did you realize that that was troublesome in that laboratory early on?

Dr. Schechter: Too late. I mean in retrospect, wasted a fair amount of time before we realized that we could not protect our tRNA and it took from the nuclease's that existed in the environment.

Dr. Margolin: That's a very interesting story, that you had to stumble through all that before you realized what was causing your problems.

Dr. Schechter: Sometimes the focus of research is affected by surprising factors. Ironically, the area that I wanted to work on became for me much less interesting over the next several years because it turned out that each amino acid had an enzyme, which was very different from that of every other one, and I was hoping when I began that work that there was just one family of very similar enzymes, and one could develop general principles of nucleic acid protein interactions. But the field became very diffuse, and very separate, and so in retrospect, I'm glad that I did not stay in that field because it never really matured in the way that I had expected and hoped at that time.

But getting back to the theme, at that point by 1974, I felt that I had to do something different, and the irony was that I was called late one Friday afternoon by an administrator in the National Heart Institute, Dr. John Hercules, who had been hired a year or two before to help manage the scientific basis of the sickle cell disease program, which had been given to the Heart Institute to oversee.

He was going to a site visit to a research program at Columbia University in New York under Cyrus Levinthal, and a protein chemist had been on the committee, but the protein chemist had withdrawn for some reason at the last moment, and Dr. Hercules wondered if I could substitute for that person. So, one ... of course, the project sounded interesting, and also because I always enjoyed visiting New York, I said yes. Late Sunday night or early Monday morning, I joined two or three other people on the train to New York and spent the next two days learning about the progress in the field of sickle cell disease, and also several approaches to the problems that were being pursued at Columbia and elsewhere.

On the train back from that site visit, it occurred to me that some of the techniques that I was developing for the immunological studies with Dr. Anfinsen were relevant to the sickle cell disease probable project. In particular, we were making short peptides from the amino acid sequence of hemoglobin to purify antibodies specific to sickle or fetal or other hemoglobin's. This was before monoclonal antibodies, and also before molecular biology techniques for prenatal diagnosis, but we had hoped that these antibodies could be used for identifying hemoglobin's, and perhaps for prenatal diagnosis. But we had the expertise using the miracle synthetic methods to synthesize large amounts of peptides of relatively short length, 10 or 15 amino acids.

It occurred to me after the site visit in New York that such peptides might act as competitive inhibitors of the aggregation of sickle hemoglobin, and thus being potential therapies for the disease. Within a few weeks, I had switched the bulk of my research program from what it had been, largely the tRNA synthesis work, and also work with peptides from Staph nuclease and micronucleus, and the more fundamental studies just seeing if we could inhibit the polymerization, or aggregation of sickle hemoglobin inside the red cell with these short peptides.

To make a two- or three-year story brief, it turned out that we could not get either high enough concentration of the peptides for sufficient entry to the red cell to make them effective as therapies. But that experience those two years, or three years of work, led me further into the sickle cell field, including being asked to be on review committees for the comprehensive sickle cell centers, which were just then being funded through a Congressional mandate by the Heart Institute.

From those experiences on review committees over two years then, and another two years a few years later, I began to see the whole field of sickle cell disease, and felt that I could write a review article on the subject that would bring some of the protein chemistry, and even the molecular genetics studies into the realm that physicians and clinicians would find relevant. Over the next year with by then Post Doctoral Fellow, Dr. Jurrien Dean, we prepared a review article, which ran in three issues of the "New England Journal of Medicine", including with color illustrations, which I think were among the first such illustrations in the "New England Journal", which tried to explain the protein chemistry and the genetic background for current approaches, with then current approaches to the therapy of that disease.

So all of those experiences, which have fallen out from the idea that peptides might be potential therapies led me further and further into the sickle cell anemia field, and with it a very strong change in my research focus for the basic studies that I had been doing with Dr. Anfinsen on peptide and protein confirmation to focus on a particular human disease, and indeed approaches to the therapy of that disease.

Dr. Margolin: It's very interesting how serendipity led you into this whole area, and how you can become an expert by working in a field that you had not known anything about before, and recognized nationally as such an expert.

Dr. Schechter: Thank you. There is a little loop in here, and I think such loops might be necessary in that by, whether coincidence or not, why I was in medical school at Columbia University in the period, 1961 to 1963. There was particularly a strong group at Columbia working on hemoglobin diseases, Helen Rany in particular, and also Vernon Ingram had come from MIT once or twice a month to lead an informal discussion group among those interested in the problems related to hemoglobin diseases.

I was fortunate to be invited or allowed to participate in that informal discussion group. So I had had some background out of the ordinary, and I think probably, I agree with your point, Dr. Margolin, that it's serendipity in all this, but I was able to go in those directions because I had had some previous experience, which was relevant.

Dr. Margolin: That's called the prepared mind.

Dr. Schechter: Yes. Thank you. Yes. But segueing now further into the directions, which the sickle cell research went, although I could probably spend several hours talking about this, I don't think anybody wants to wade through all that at this moment. I will say that among the studies that evolved in the early 1980s was attempts to treat sickle cell anemia patients by increasing the levels of fetal hemoglobin.

Dr. Margolin: This was an attempt to treat the painful episodes primarily, not the full disease?

Dr. Schechter: Well, we hoped then, and ironically probably is not worked out, but I'll come to this a little later, that increasing fetal hemoglobin would be enough to be an effective therapy, if not curative, for all the manifestations of sickle cell disease, both the painful crises and the organ damage, and the premature death.

Dr. Margolin: Mm-hmm (affirmative).

Dr. Schechter: But then to relate this to my work in the late 1970s on the peptide inhibitors of hemoglobin polymerization, we in the late 1970s working with Dr. Constance Noguchi and Dennis Torchia developed NMR, nuclear magnetic resonance methods, to study the intracellular polymerization of sickle hemoglobin. Again, this is an example of the loop or the prepared mind in that my earlier studies on protein folding with Dr. Anfinsen, and also some studies independently done while I was in Dr. Nansen's laboratory.

We had used various new NMR techniques to study protein structure. So, therefore, I knew the NMR Community, and I was moderately familiar with the basis of the techniques. So when we realized there was an important problem, which was solved, we could find one or more investigators to work with us to adapt NMR techniques to answer the question we wished to ask.

Dr. Margolin: Were those people here on the grounds of NIH?

Dr. Schechter: Yes. Yes.

Dr. Margolin: That was an advantage that wasn't ...

Dr. Schechter: Yes, one other thing. I recently read several chapters from a book being prepared on the research associate program in the late 1960s by Dr. Raymond Greenberg of the University of Texas Medical Schools, and Dr. Greenberg in his book points out the fact that there was so much activity at NIH compared to almost any individual medical center, or even perhaps one or two major research institutions that one could find collaborators in vast numbers of fields on the NIH campus. This facilitated a lot of new directions of work for people who came in the 60s and the 70s.

But, again getting back to the theme, which we've regressed from in many, may ways is that in the late 1940s a physician at Downstate Medical School in Brooklyn, New York, named Chad Watson, had observed that children with sickle cell disease did not begin to manifest the illness until they were six months of age or older. She realized that the different hemoglobin that predominated in the red cells of newborns was now susceptible to the same processes that was disease as was the hemoglobin in sickle cell anemia children after the age of one or two.

That led to the realization that this other hemoglobin, so called fetal hemoglobin, which persists for many months after birth and longer periods in sickle cell children, is protective against the effects of the small amounts than of the sickle hemoglobin or acts as a protective until its levels get very low. In the first studies of sickle cell disease that were done on an epidemiological basis in the period after the emphasis on that disease occurred in the early 70s with the push for a large program at the NIH, evidence was found that the fetal hemoglobin level ... that fetal hemoglobin levels were indeed protective of complications from sickle cell disease.

So there was interest in developing methods to prevent the turning off of fetal hemoglobin after birth or to increase it in adults. This led the Heart Institute, I think it was the National Heart Institute then, later becoming the Heart, Lung and Blood Institute, to issue a request for proposals or requests for applications for work on fetal hemoglobin, which began a nationwide push in this area and we were also interested in that, although we did not ...

PART 1 OF 5 ENDS [00:32:04]

... also interested in that, although we did not have a particular viable approach to increasing fetal hemoglobin. Fortunately, a group at the University of Illinois in Chicago, under Doctor Paul Heller, who was a prominent hematologist, a refugee after the Second World War from Czechoslovakia, established a nonhuman primate colony at the University of Illinois. And began to attempt to treat pharmacologically, or other ways, the nonhuman primates to increase the levels of fetal hemoglobin in these animals. And as a result of a complicated story, they injected the animals, I think they were the baboons, with 5-Azacytidine, a drug that was known to change the methylation pattern of DNA in erythroid cells, and found a significant increase in the fetal hemoglobin levels in these baboons.

Doctor Heller, with his colleague, Doctor [Joseph DeSimone 00:33:22], came to NIH in the early 80s to discuss with Doctor Arthur [Nienhuis 00:33:30], who was then ... Well, it was the Heart, Lung, and Blood Institute, and who maintained a large clinic basis of sickle cell patients, largely because a Doctor Robert [Winslow 00:33:46] had been at NIH a few years earlier and was studying oxygen transport in sickle red cells. And although he left, Doctor Nienhuis maintained the clinic, largely as a adapted teaching function for the residents and fellows in hematology, not because there was a robust research program any longer in the Heart Institute.

But fortunately Doctor Nienhuis, having a large cohort, or a moderately large cohort, of patients and an interest in this field, found the work on 5-Azacytidine from Chicago very interesting. And he contacted me, knowing that I was actively working in the sickle cell field, and we began joint projects which lasted for about a decade, as long as Doctor Nienhuis was still here at the NIH. And the first one was to treat a small number of sickle cell patients with 5-Azacytidine. He also, and this was independent of any contribution of mine, had a clinic focused on thalassemia, which was his real interest. And the 5-Azacytidine, although it had originally been prescribed for a sickle cell disease, was also relevant to the potential treatment of thalassemia.

And so patient protocols began in the early 80s here. We went through the IRB process, because fortunately Doctor [Griffin Rogers 00:35:31] had just joined my research program, more to work on cellular aspects, so sickle cell red-cell aspects of sickle cell disease, but was a very well-trained hematologist, well trained physician, who later trained in hematology. And he was the person who wrote the protocols for the sickle cell treatment studies that we did over the next 10 years or so. And we found that the 5-Azacytidine was quite effective in the sickle cell patients, and to some extent in certain thalassemia patients.

But also there was large push back from the larger community, especially for example Doctor [Wetherall 00:36:31] in England, who felt that 5-Azacytidine was potentially too dangerous to use chronically in patients who might have a serious but less severe illness than 5-Azacytidine had been used to treat in other circumstances. And so there was a lot of dissension within the larger community of whether the results we were getting with 5-Azacytidine was sufficiently robust to justify the potential risk of using this drug.

Dr. Margolin: What kind of findings were you getting in terms of the value to the sickle cell patient?

Dr. Schechter: Okay. There were only a few sickle cell patients done, but some responded with a very large increase in fetal hemoglobin. I don't remember now whether it was 15 or 20%, but some patients responded. We were following primarily the increase in F cells.

Dr. Margolin: I see.

Dr. Schechter: And that was very strong.

Dr. Margolin: But not the clinical changes in the patient or the-

Dr. Schechter: The studies were all short-term of giving the drug for a few days or a week or two just to see whether there was an effect in the right direction. But they were no clinical studies done other than measuring changes in the blood parameters.

Dr. Margolin: Okay.

Dr. Schechter: That was the story in 1983 and '84, perhaps almost 20 years after I had come to the NIH. But again a serendipitous finding occurred at that point, but this time in Boston, when David [Nathan 00:38:21] and his colleagues observed that children being treated with hydroxyurea had some elevation of fetal hemoglobin.

Dr. Margolin: What were they using the hydroxyurea for?

Dr. Schechter: I think for neoplastic diseases. The children were being-

Dr. Margolin: It's an antimetaboliter, a protective, yes.

Dr. Schechter: It was used extensively then for polycythemia vera, but it was also used for myeloproliferative diseases of various kinds at that point. But that led the Boston group to work with the Primate Center near Boston, and showed, similar to the work to the work that had gone on at the University of Illinois, that primates responded to hydroxyurea with significant increases in fetal hemoglobin. Which then again led to the desire to try this in patients, both thalassemia and sickle cell patients. The hydroxyurea was much less potent on a milligram basis, or on an accepted dose basis, than 5-Azacytidine. But it was also felt to be less dangerous, and so therefore the protocols that we and others did had a longer duration and were able to begin to look at some of the clinical manifestations as well as the hematological manifestations.

Ironically, when the Boston group did some clinical studies in patients with hydroxyurea they got very poor responses, and probably they were using much too high doses, and they were therefore blunting their own responses. We, and this was really Doctor Rogers' insight, began with very low doses of hydroxyurea and gradually escalated the doses over several months of administration. And we were able to do this because all the patients ... In the first major study there were 10 patients who followed each for three months or more. The patients could, because of the unusual nature of the NIH Clinical Center, be hospitalized here for three months, and therefore acceptance of the drug and use as well as escalation doses could be very rigorously followed.

A similar clinical study was done on the clinical research unit at Johns Hopkins at about that time, also using relatively small doses. Again, ironically, the advances that occurred in that period, which I think were from 1985 to 1988 or '89, were largely done in freestanding clinical research units, like the NIH Clinical Center or the clinical research unit at Hopkins, and not through NIH extramural grants. The study sections, the review committees, were very leery about funding such research, they thought it was to apply, and investigators having a very difficult time getting any funding for clinical studies. And this is something that perhaps we can come back to when we talk about the NIH preferences.

Dr. Margolin: Yes.

Dr. Schechter: But the advances that occurred came because of the ongoing freestanding clinical research units. And we and the Hopkins group found that the hydroxyurea did increase fetal hemoglobin very significantly. Although, ironically, we found that one third or 25 or a quarter of the patients had no response to the hydroxyurea. And another third had only small responses. So it seemed likely to us that only a sub-fraction of all the patients would respond vigorously enough to the hydroxyurea. The Hopkins group at first objected to our interpretation of the results, but I think eventually they came to realize that our findings were indeed valid. And this will come back to something that I'll talk about in a few minutes.

But the results that we obtained, and that were obtained at Johns Hopkins, led NIH, the Heart Institute or Heart, Lung, and Blood Institute eventually in the early 90s to fund a multicenter study of hydroxyurea. Which was done with, I believe, 200 patients, and 200 who were treated and 200 patients who acted as controls, in 10 or 15 medical centers around the country. And that study was stopped early in 1993 or '94 when the first results were obtained which showed decreased hospitalization and decreased blood transfusion in the patients being treated. And a publication describing these results appeared in a journal with Doctor Samuel [inaudible 00:44:19], first author, in 1995, and led to the approval by the FDA in 1998 of the use of hydroxyurea for severely ill sickle cell patients.

Dr. Margolin: Was it being given just at the time of the illness, or was it given chronically?

Dr. Schechter: No, being given chronically.

Dr. Margolin: Chronically.

Dr. Schechter: Yes.

Dr. Margolin: And it affected the whole entire segment of sickle cell, or just a fraction?

Dr. Schechter: That's still to this day not clear, unfortunately. One of the ironies ... And I was not happy that it was decided to end the study early before the expected time of the full duration, as had been planned. And painful crisis was one of the prime factors being measured, but also things like hospitalization rate, blood transfusions, episodes of acute chest syndrome, and the like. And two or three of the criteria, the endpoints that had been adopted, including pain and hospitalization and blood transfusions, I believe, all showed benefit. But the study was not carried out long enough to know if mortality was changed, nor was it carried out long enough to know whether factors such as lung disease or renal disease or other complications also were improved. And to this day it is really not known whether the hydroxyurea, even in those patients who do respond well with moderate to large increase in fetal hemoglobin, have protection against all the aspects of the disease.

Dr. Margolin: As I understand, hydroxyurea is still being used, it's approved, and it's used on a chronic basis in a large segment of the sickle cell population. As far as you know?

Dr. Schechter: The first two aspects of your statement are true, but unfortunately not the third. As of 10 years ago there was data suggesting that only about 5% of the sickle cell patients in the country, especially adults, were getting hydroxyurea. And probably a larger number in children who were followed in pediatric centers. But once individuals are not in major centers and are being followed by physicians or hospitals or individual communities the use of hydroxyurea is probably far sub optimal.

Dr. Margolin: How often did it have to be given on a chronic basis?

Dr. Schechter: I think daily, with a dose which is an optimal dose, which is determined by slow escalation and monitoring white blood cell count and platelet count for evidences of hematological toxicity. And a chronic dose is established that is felt to be hematologically safe but optimizes the increase in fetal hemoglobin. Ironically, I think there's a major misconception in the field, which has existed for 20 years, and which has markedly hindered the field. And I think it's a ironic byproduct of the NIH system in that the community to this day does not accept fully that increasing fetal hemoglobin is the prime beneficial mechanism of hydroxyurea. There are probably some other mechanisms but whether they're clinically significant, and even how important they are at all, is uncertain.

And the fact that hydroxyurea was developed because of the search for increasing fetal hemoglobin, and correlates best with increased fetal hemoglobin for a whole variety of reasons, including some mis-studies that were done early on or individuals finding that hydroxyurea also affected any of several dozen other parameters, the mechanism of action has been blurred in the minds of physicians, both academic and practicing physicians. And therefore, fetal hemoglobin levels are not always, or even frequently, measured in terms of the response to hydroxyurea therapy. And I personally think this is a major, major mistake. And physicians very often will start the hydroxyurea but make no attempt to follow its effect on fetal hemoglobin, and if the patient does not perceive he or she is better it may very well stop the hydroxyurea. And this may in part account for what was a usage of only 5 or 10% a few years ago.

There is in the corridor outside of where we are having this discussion a poster from a meeting that was held here at NIH 10 years ago on hydroxyurea. The goal was to increase the use of hydroxyurea, but ironically, at that whole meeting, which I attended, it was decided that one would not even discuss at all the mechanism of hydroxyurea. For me it was like talking about antihypertensive agents and not being allowed to mention blood pressure at all. I think our field has not shown very encouraging intellectual honesty in the hydroxyurea story, and I think the patients are suffering because of this.

Dr. Margolin: Was it given orally?

Dr. Schechter: It was given orally.

Dr. Margolin: As a tablet or powder or something?

Dr. Schechter: Yes, a tablet.

Dr. Margolin: As a tablet. It wasn't very expensive was it?

Dr. Schechter: No. That is another irony, since it's off-patent there has not been ... Although I think Squibb that applied for the FDA approval and manufactures it. But there was never really a big push for its use because the medication was so inexpensive that it [inaudible 00:51:07], unlike modern cancer drugs or other drugs.

Dr. Margolin: When I was clinically active, I saw it being used for acute crises, I didn't recognize it as being used on a chronic basis.

Dr. Schechter: No. That probably was another misconception. I think having been in the field since the first day in the early 80s, and having watched it evolve, I've been appalled by the misconceptions that have emerged in the field. One of the ironies about medicine in this country, as for example compared to other countries, is there really are no committees or individuals to make policies or to decide that something is right or not right, and so individual beliefs or regional differences permeate the system, and so very often it takes many years, decades, for things to be adapted or other things to fall out of favor.

Dr. Margolin: Well, I think that's a very common problem in medicine in general which you're expressing. It looks like you'll have to form a new committee.

Dr. Schechter: Yes.

Dr. Margolin: Okay, all right.

Dr. Schechter: To summarize what I've just said, is that in 1995 the results of the multicenter hydroxyurea trial were published, which showed benefit in certain criteria that were used. Although the trial was ended early, and some of the most important endpoints were not established. Unfortunately, a problem that exists to this day. But in 1998 the FDA approved hydroxyurea, and there was then a lot of interest in finding other drugs which might increase fetal hemoglobin in more patients, so those who did not respond to hydroxyurea, or to a greater extent than was the case.

And I should mention in answer to the question that Doctor [inaudible 00:53:27] asked earlier, that even to this day it seems that some manifestations of disease such as the pulmonary aspects may not respond well to increases in fetal hemoglobin as well as the painful crises or blood transfusions. And so there has been in the field the belief that there are groups of manifestations or symptoms that may relate to different mechanisms, and therefore the benefit one gets with increasing fetal hemoglobin may not map equally on all clinical manifestations. But that's still not clearly understood 25 years after the first major [crosstalk 00:54:16].

Dr. Margolin: But in studying the molecular nature of sickle cell, are you finding all the patients having the same alterations?

Dr. Schechter: Yes.

Dr. Margolin: As you measure them?

Dr. Schechter: Okay, well, that's a very interesting question which opens up a whole range of questions. Many or most genetic diseases, which are due to single mutations, so-called Mendelian diseases, are very homogenous, and patients have similar manifestations at similar ages, and the severity is similar. Some diseases, as we've learned more about them, such as cystic fibrosis, are found to be more heterogeneous, though not fully appreciated in part because the different mutations of the conductance protein have different effects.

Thalassemia, which is the other hemoglobin disease which has been of the greatest interest, has always been realized to be very heterogeneous. And that clearly was understood in the 70s and subsequently as the basis of the thalassemic syndromes were worked out. First the difference between alpha and beta thalassemia. And then within each the heterogeneous of where the mutation was, or the number of genes that were affected, and the like.

But sickle cell disease has been ironic as compared to all those syndromes, because all the diseases are of a single mutation, the beta 6 valine substitution for the normal glutamic acid. But ironically, the severity varies immensely from children who die in the first year of life to individuals who are sufficiently well that they serve a full military service and are only discovered in the military or subsequently. My wife, as head of hematology at the Veterans Administration hospital, has treated several patients who have not realized that they were sickle cell anemia patients until their 20s or 30s.

This heterogeneity has made therapies such as bone marrow transplantation difficult to plan because one does not necessarily know early on how severe a given individual will be, and whether they should get difficult or risky therapies. On the other hand, the basis for the heterogeneity is equally obscure that people have looked for modifying genes, or other factors in the environment, or perhaps epigenetic factors, and the like. But the heterogeneity has remained a very intractable problem in sickle cell disease, and they also contribute to the non-universality of the effectiveness of hydroxyurea or other therapies.

Dr. Margolin: Well, that makes clinical studies very difficult to do, and to answer the question that you asked before, and why we're not further along with it.

Dr. Schechter: That is correct. Yes. Yes, I agree that that is a very difficult question. As listeners or readers will know this is all ironic because it was in 1948 that Linus Pauling and his colleagues called this the first molecular disease.

Dr. Margolin: [inaudible 00:58:12].

Dr. Schechter: And it was expected as the amino acid mutation was discovered by Vernon Ingram, and other progress was made in the 60s and 70s, that an effective therapy would be forthcoming given the relatively simple nature of the genetic basis of the disease. But that has not turned out to be true even when large amounts of resources were focused on understanding or treating the condition.

But in terms of my own story I think this is a point to mention, that in the late 1990s after our studies with Doctor Rogers and Doctor [Noguchi 00:59:09] and others, and many postdoctoral fellows who came, fortunately for me, to work with me during those years, I was unsure of the direction that my own research should take. In the 1990s I focused on studying the beta globin genes with an idea that that study of transcription factors would help us identify either how 5-Azacytidine and hydroxyurea worked or would lead us in the direction of finding new drugs that would be effective.

And I was part of a international group, who are colloquially referred to as the hemoglobin switching people, and every two years since 1978 or '79 there has been a so-called hemoglobin switching meeting in which 150 or so individuals get together to talk about the latest results, almost all focused on the transcriptional control of globin genes. And despite several major advances in this field, such as identification of a strong promoter, or enhancer I should say, in the beta globin gene cluster and the indemnification of the so-called [Gada 01:00:43] proteins, as being important in the control of all erythroid genes, and a few other discoveries which have had general implications, the work of the hemoglobin switching field has not really led to significant increases in understanding the mechanism of transcriptional control or the normal ontogeny of the globin genes. What controls the turning off of fetal hemoglobin and the turning on of the beta globin genes.

And the progress, both at a molecular level and a clinical level, a therapeutic level, have been much, much slower than anybody has expected despite the fact that the group of people who, in part almost the same people since the beginning, continue to meet and continue to try to push their field further. But with not that impressive application, development of new applications in the basic science.

But my own story relates to this in that when I had a review by the Board of Scientific Counselors in the mid or little later 1990s, the counselors said that my research program was good; not very, very good, but very good. But that the field of the control of globin genes was not moving very fast, and they wondered why I continued to work in that area. And my initial reaction was one of being negative about the outside counselors because my interest was the clinical application, and even if the field had not moved that fast in the preceding 10 years that was not a reason for going away from it. In fact, if anything, from a practical application, from a clinical application, I thought the counselors were absurd, because that was all the more reason to stay in it and try to change the situation.

But I was sensitive to this feeling on the part of outsiders. And in 1998 a major break came for me, in two ways. One is that I was asked to referee a paper for the Journal of Clinical Investigation from a group at the Massachusetts General Hospital on potential use of inhaled nitric oxide in treating sickle cell patients. And although I was skeptical of the paper and recommended rejection, the Journal decided to publish it, but asked me to write a covering commentary on the paper. Which I did by spending a weekend here in this very NIH library reading the nitric oxide literature, which I hardly knew at all-

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Nitric oxide literature, which I hardly knew at all of 1998 although very shortly thereafter the three individuals who identified nitric oxide as an important biological gas, shared the Nobel Prize. Shortly thereafter nitric oxide became the so-called "Molecule of the Year" in Science Magazine, and so it was a heady time for nitric oxide. I think at that time, I did a survey and there were more than 25000 publications on nitric oxide, which I could not read in their entirety that weekend here in the library, but I read enough of them to write a commentary in The Journal of Clinical Investigation mildly poo-pooing the paper that they were publishing which turned out to be incorrect as I suspected.

Also at that point in 1998, a young physician, MD-PhD, came to the Critical Care Medicine Department of NIH to have a research career here at NIH named Mark Gladwin. Mark, who had trained in pulmonary and critical care medicine both here a NIH and in Oregon and Washington State afterwards, had reasons still not clear to me an interest in both sickle cell disease and nitric oxide because in his past experiences in using nitric oxide in critical care medicine and sickle cells is, I think, because he was brought up in Florida in a community in which there were many sickle cell patients who went to medical school in Florida.

Mark, once he established himself in the fall of 1998, looked around for somebody to work with in the two area of sickle cell disease and nitric oxide, and Dr. Rodgers and others pointed out to him that I had been interested in both fields, so he came to see me. And what turned out to be almost a decade long collaboration was started between Dr. Gladwin, Mark Gladwin, and myself. Our first field investigation was to repeat the work that had been reported for The Massachusetts General Hospital. At that time, again, doing clinical work was relatively simple compared to now. Mark was very good at writing a clinical protocol and getting it through the IRB in a month or two. And so within a few months, we could start clinical studies.

In addition, I ordered equipment for my laboratory to measure nitric oxide and the like and made some space available for Mark and for several post-doctoral fellows that we recruited. Should mention that being in critical care medicine by the convention of NIH, Dr. Gladwin was not supposed to have a research career, but it's always been important and necessary to recruit good people to the clinical center unit such as the blood bank, now called The Division of Transfusion Medicine or critical care medicine or others that these individuals have access to research programs. The compromise that was worked out, this is part the genius of Henry Masur, who has been the longtime leader of the critical care medicine. Dr. Masur will use resources, including personnel, to facilitate or promote the research enterprises of his investigators, but I had the space and the ability to buy equipment that was not so easily available to Dr. Gladwin; and so therefore, we became a team early on.

In some ways, I was actually Dr. Gladwin's mentor for the first year or two. He was perhaps one of my two or three most spectacular mentees, and clearly was the leader in our collaboration from early on that he had the ability to read widely, to understand things, a medical background, a clinical background that I did not have, and the like. So we decided, eventually within a year or so, practically everything either of us was doing was in collaboration. As I mentioned, the first test we did was to test the work from that had been reported from Massachusetts General Hospital. And as we expected, we found it to be incorrect, and I think we understood the artifacts that had occurred.

But in order to do this, we had to set up, in my laboratory, assays for measuring nitric oxide, nitrite, and nitrate ion levels. The other aspect that had developed in the nitric oxide field during those years, was that a group at Duke University had reported that nitric oxide could bind to the beta-93-cysteine residue on hemoglobin in a reversible fashion, and that, when the oxygen levels were high, the nitric oxide would bind. When the oxygen level were low, when the deoxy form of hemoglobin, the nitric oxide, would also come off. The Duke University group under Jonathan Stamler proposed that this hemoglobin intermediate called snow hemoglobin or s-nitroso-hemoglobin was a way which nitric oxide could be transported from one organ to another or could be used therapeutically for example with nitric oxide inhalation that the nitric oxide bio-activity, which would lead to vasodilatation and increased blood flow could be transported from oxygenated organs to hypoxic organs. This work on s-nitrosation of hemoglobin was published in Science and Nature and PNAS and was widely accepted as a major breakthrough in the field.

And it was on this basis that we wanted to treat sickle cell patients with nitric oxide.

Dr. Margolin: I see. So the theory of using in sickle cell was simply to increase blood flow in the areas that were ... the blood flow was impaired?

Dr. Schechter: Correct. And that, as we knew, going back 40 or 50 years was really the basis of the pathophysiology of sickle cell. Where the rigid cells, which had aggregated hemoglobin would obstruct blood flow.

I should mention, the one transition that I didn't state when I began to talk about what happened in 1998, was that by that time in 1998, even though the FDA approved the drug, I realized that it did not work on all patients and even those patients that it did have some beneficial effect. The beneficial effect was not sufficient to ameliorate all manifestations of the disease; and so therefore, I was looking for an alternative way of developing a therapy for sickle cell disease. As well following the mandate of the outside counselors, I was looking for new horizons to work in.

Dr. Margolin: So it turns out the use ... your concern about the use of nitric oxide had nothing to do with changing the hemoglobin in any way. It was merely a blood flow phenomenon which was inherent in the disease of course.

Dr. Schechter: Correct.

Dr. Margolin: Okay.

Dr. Schechter: That is right.

Dr. Margolin: Makes sense.

Dr. Schechter: Ironically, there is some weak evidence, some of which we contributed to, that nitric oxide or nitric oxide donor compounds can increase fetal hemoglobin, but that effect is very small, and I don't think is really a major factor. Our papers on the subject have been widely cited, but I've never felt they were really that important.

Our goal was to try to develop the nitric oxide therapy. It had been approved in the 90's for use in newborns with respiratory distress, and companies were manufacturing nitric oxide inhalation apparatus that could be used for newborns to get nitric oxide therapy. We were primarily struck by the work from Duke that said that here was the mechanism. But the other thing in addition to trying to repeat the studies that had published on the use in the sickle cell patients, we wanted to confirm the work from Duke that snow hemoglobin did form. That beta-93 has been of interest to hemoglobin students for many years since it's highly conserved in virtually every mammalian and even the hemoglobin of other vertebrates. It's function, the beta-93 sulfide group, it's function has not been fully understood despite this extraordinarily high degree of evolutionary conservation.

In addition to doing clinical studies that I mentioned, Dr. Gladwin and I about those first were on six or eight normal volunteers who inhaled the nitric oxide ... I'm sorry. I'm incorrect. Those first studies were done on half-a-dozen sickle cell patients who inhaled the nitric oxide, and we could not confirm the results which were reported. But then, we wanted to test the Duke University hypothesis that of Stamler and his colleagues. I think, in addition to setting up a research laboratory that I and Dr. Gladwin could use, one of my contributions to the initial work was to emphasize that we had to focus on normal volunteers and not on sickle cell patients. That until we understood the effects of nitric oxide inhalation or administration in other ways, on normal volunteers, we could not understand what was happening in sickle cell patients.

From the period of 1999 or 2000 until about 2005, the vast bulk of my work was done with normal volunteers, either normal blood or clinical studies with these normal individuals. I think this has been a strong belief of mine. That unless you understand what happens in normal, you can't really understand what happens in diseased states.

I should mention, in terms of another generality that I would like to make, among the 25000 publications that I was aware of, not having studied many in detail. At that period in 1998 or 1999, the vast, vast majority, probably 95 or 98% were on nitric oxide either in cells or with molecules or with experimental animals. And the number of individuals anywhere, in the United States or elsewhere, studying nitric oxide metabolism and effects in human beings were in the dozens or hundreds at the most. And so the field, as so many other fields in biomedicine, quickly became dominated by mechanistic studies and animal studies, and not clinical studies. I think the contributions we made to the field, which I think, and I'll come to in a moment, were significant came because our focus from the very beginning was always on human beings either normal volunteers or sickle cell patients.

Getting back to the chronology in the period from 2000 to 2002, we came to the conclusion that the Stamler hypothesis was incorrect. That snow hemoglobin levels were probably one tenth or one hundredth that being reported by the Duke University group. The formation of snow hemoglobin was not a major way of transport of nitric oxide, and we think that was artifacts in the way they were measuring the nitric oxide level. They were also primarily focused on experimental animals. It's possible, probably less likely, the levels were higher in the experimental animals. So on the one hand, and I should say that Dr. Gladwin was very intellectually honest, and one day we'd go over the results and he'd feel he had confirmed the snow hemoglobin hypothesis, and the next week it looked like we had not. And after a year or two of going back and forth, we finally concluded that we could not confirm the hypothesis.

However, I think an alternative arose in our discussions. And I should say that Gladwin and I would have coffee at least once or twice a week in the atrium here in the clinical center, which had just opened then. And in these long coffee discussions, any ideas that we ever had came out. I think the point of science being a social activity and being able to talk over it is crucially important. That was in part what made our collaboration so good and so effective I think. And during one of these conversations, we came to realize that although the Stamler hypothesis, we believed, was incorrect, there was evidence that nitric oxide bio-activity could be transported in the body like a hormone. It had endocrine effects. We did not think it was being transported on the hemoglobin molecule, but rather we came to the conclusion that it was being transported as the nitrite ion.

Dr. Margolin: In solution in the plasma?

Dr. Schechter: In solution in the plasma, correct.

That until about 40 years ago, it was thought that nitrite and nitrate NO_2^- and NO_3^- were irreversible oxidation products of nitrogen metabolism and were excreted in the urine and were of no biological interest. Ironically, an investigator named Peter Goldman, who was then at NIH, published a paper in Science about then showing that the mammalian body, I think humans, but it may have been other mammalian tissue, could synthesize nitrite and nitrate. This was an incidental finding of his. I was aware of it at the time, but had little interest in it, did not pay any attention.

But that really, in retrospect, changed the field because suddenly we thought of nitrite and nitrate as part of metabolic processes in the human, not just as irreversible oxidation products. By the time we were working in the nitric oxide field, the NO field, we were aware that nitric oxide could be after it was formed by nitric oxide synthase enzymes, which were the major focus of mechanistic studies in the NO field in the 1990's. After the nitric oxide was formed, it could be oxidized by heme-proteins, hemoglobin for example, to nitrate ions or, to a lesser extent, to nitrite ions.

During the course of our work, we made the hypothesis that, and this came actually from our discussions over coffee, that nitrite reduction by deoxy-heme-proteins might be the way that nitric oxide bio-activity is transported in the blood stream from one organ to the other. Or when one inhales nitric oxide, we found in normal humans again that nitric oxide bio-activity could be detected, for example, while inhaling nitric oxide, if one inhibits the endogenous nitric oxide synthase enzymes in the arm of a normal volunteer, one can show that the inhalation of nitric oxide increases blood flow in that arm.

We saw that there were systemic effects of inhaled NO. We hypothesized that this was coming from nitrite ions. After 2003, nitrite ions became the center focus of our research. We showed a number of mechanisms by which nitrite could be reduced to nitric oxide in mammalian tissue, or in human beings, or in experimental animals. This, I think, was our major contribution to the NO field.

Dr. Margolin: I see. The nitric oxide is vaporized and can be inhaled and absorbed, is that what you're saying?

Dr. Schechter: Yes. One can buy cylinders of compressed nitric oxide-

Dr. Margolin: As a gas?

Dr. Schechter: -as a gas, and companies have devised inhalation devices using these cylinders of compressed nitric oxide for therapies. They're used for newborns and, to some extent, adults with respiratory distress.

Dr. Margolin: I see. So you could get the nitric oxide in as a gas, and then expect it to be reduced by the enzymes in the body-

Dr. Schechter: No. The other way. That the nitric oxide that's either formed by the nitric oxide synthase enzymes in the body, or that are administered in gas are oxidized to nitrite and nitrate. We showed that the body could, in turn, reverse that and reduce the nitrite back to NO. We now believe that probably as much nitric oxide is produced in the body by reduction from nitrate as is produced by de novo synthesis from arginine by nitric oxide synthase enzymes.

Dr. Margolin: So you don't need the inhalation techniques to get it into the body?

Dr. Schechter: Yes. We have, Gladwin and I with Richard Cannon who was then Clinical Director of the Huntsman who participated in many of our first clinical studies, have a patent via the NIH for the use of nitrite ions by inhalation or infusion as a source of nitric oxide. Although 90% of the NO field is still focused on the nitric oxide synthase pathway, we and others have emphasized, in the last 10 or 15 years, the reductive pathway in which nitrite forms NO. I should mention that at the same time we were doing these studies, a very good group in Stockholm, Sweden, Lundberg and Voitsburg had shown that bacteria in the saliva can reduce nitrate, NO3-, to nitrite, and the nitrite could then be reduced to NO.

Most of nitrate reduction is bacterial. I'll mention a little later that we have some evidence that some nitrate reduction can also occur in some mammalian tissues. But what we focused on for about 10 years was the nitrite reduction. I think we made a significant contribution in the field and helped begin the realization that as much as synthesis by the three classes of nitric oxide synthase enzymes, reduction of nitrate and nitrite are also major sources of NO bio-activity in the body.

Dr. Margolin: Okay. So the mechanism, having been established by you and you're comfortable with it, was that applied then to sickle cell, and has it made a difference?

Dr. Schechter: Yes. That's a very good question. That is both an irony and a disappointment in that when we tried to administer NO either by inhalation or by nitrite infusion to sickle cell patients, we got effects which were much smaller than those in normal volunteers. We were puzzled by this.

Dr. Margolin: Smaller in terms of blood flow? Regional blood flow?

Dr. Schechter: In terms of regional blood flow.

Dr. Margolin: What regions were you studying?

Dr. Schechter: The arm. We would measure blood flow in the arm with a screen gauge.

Dr. Margolin: Okay. So that was the main end point?

Dr. Schechter: Yes. But the first studies with Dr. Cannon showed that the sickle cell effects were much smaller, and this was, in many ways, a big disappointment, but in turn opened up a whole new field because Dr. Gladwin and I realized that what was different in the sickle cell patients, in addition to the sickle red cells and the like, was that most sickle cell disease patients had significant amounts of cell-free hemoglobin in the circulation from hemolysis of sickle red cells. And the sickle cell patients one saturates the haptoglobin and the hemopexin easily, and one has, although it's very variable from patient to patient and may vary with the clinical state, there is significant amounts of cell-free hemoglobin circulating. We, and others before us, had shown that cell-free hemoglobin destroys nitric oxide much more readily than the hemoglobin inside the red cell. There are diffusion barriers of the hemoglobin inside the red cell which are not effective in cell-free hemoglobin.

Dr. Gladwin, and this was work largely done not in collaboration with me but on his own with other investigators, have shown that levels of cell-free hemoglobin can predict, to some extent, the severity of the sickle syndromes and the clinical manifestations. He has argued that you could divide the sickle syndromes of sickle cell anemia individuals into those with primarily one or the other syndrome complexes due to levels of cell-free hemoglobin.

Dr. Margolin: That takes away your concern about the variability.

Dr. Schechter: Yes. That probably contributes to the variability, but that's probably only one of many factors.

Dr. Margolin: I'm sure. But you fell into one answer that seemed very comfortable to you because it's measurable.

Dr. Schechter: Yes. But your question is very perceptive because we started all this in 1998 with the goal: first, based upon the work from Boston, then the work of Stamler, and then our own work, thinking that the nitric oxide would become either as nitric oxide or as nitrite, a therapy, but nature kept on putting up barriers for us. Our data did not support our original hypotheses.

Dr. Margolin: So it isn't, at the moment, nitrates are not used for sickle cell anemia, but are you doing anything to keep the hemoglobin from hemolyzing to the extent where they become barrier for the nitrates?

Dr. Schechter: The NIH has funded research on trying to look for decreasing hemolysis. Most active, for example, just in stored blood in the blood bank because after a few weeks of storage the amount of hemolysis accumulates-

Dr. Margolin: Even in normal blood?

Dr. Schechter: Even in normal blood. So trying to minimize the amount of hemolyzed blood that's transformed. On the other way, Gladwin and Dr. Kim-Shapiro at Wake Forest, and others, have been interested in haptoglobin or hemopexin. There's a company in Switzerland that's funded some studies on haptoglobin-hemopexin to try to reduce levels of cell-free hemoglobin with cell-free heme in the sickle cell patients as a therapeutic approach in order, presumably, the cell-free hemoglobin or free-heme or free-ion are destroying the endogenous nitric oxide or the endogenous nitrite, and may, themselves, to the pathophysiology.

Ironically, the work that we started with a therapeutic goal has led us to, what we believe, is other mechanism of disease. I should better state what I said in the somewhat confused way a few minutes ago, the idea that Dr. Gladwin and several of his colleagues have pushed or encouraged, although there's pushback, for the last ten years is that the levels of the cell-free hemoglobin contribute to the symptom complex by how much endogenous nitric oxide is being destroyed in the patient.

Dr. Margolin: And you can't overcome that by flooding the system with more nitric oxide.

Dr. Schechter: The problem is that the NO or the nitrite have toxicities. If you go too high, you form methemoglobin. Also if you go too high, the blood pressure can fall out. There's a very narrow therapeutic-to-toxic window; and therefore, flooding-

Dr. Margolin: But that's even though the nitric oxide is being blocked or absorbed by the free-hemoglobin or the hemopexin?

Dr. Schechter: Yes.

Dr. Margolin: Interesting.

Dr. Schechter: You have to administer it continuously and the effects when the nitric oxide does lower blood pressure to a greater extent than expected, it very often takes several hours for it to return.

Dr. Margolin: Oh. You overwhelm the system.

Dr. Schechter: It's not that you can just turn it off and reverse that. There are reasons to be worried about the potential therapeutic utility.

Dr. Margolin: Has this led then to an approach to try and reduce the hemolysis as a major attempt to-

Dr. Schechter: I think there is really no ... I don't think there are good ideas of how you could explicitly affect in vivo hemolysis. You can affect in vitro hemolysis. You can use storage solutions for blood or things like that, but in vivo hemolysis is not.

Dr. Margolin: But do you think that sickle cell patients hemolyze more from their sickle cells than they do from their normal cells?

Dr. Schechter: Yes. That's been known for a long time. I should mention in all honesty that any application of the patent that I mentioned earlier is very much affected by these complex-

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... effected by these complexities of nitrite or nitric oxide administration. That the toxicity is real and the effects, I mean it may be different from individual to individual.

Dr. Margolin: Well you think the free hemoglobin in this large quantity, or hemoglobin products, this large quantity may have something to do with kidney disease and lung disease?

Dr. Schechter: Yes. There are groups both at the FDA now, Dr. [inaudible 01:36:30] and some of his present and former colleagues, and a group in Zurich, Switzerland, Dominic [Shear 01:36:41], who believe that extravasation of hemoglobin into organs, especially the kidney, contributes greatly to the pathology by stealing nitric oxide from the kidney tissues.

Dr. Margolin: As a mechanism stealing nitric oxide. But myoglobin, for example, is very toxic to renal cells. I don't know about free hemoglobin. I think that's [inaudible 01:37:07] some toxicity, direct toxicity. What you've found here ties up with other aspects of the sickle cell disease mechanisms.

Dr. Schechter: Yes. There is controversy in the field. Gladwin originally postulated that the depletion of nitric oxide and nitrite by cell free hemoglobin occurred in the vascular system. The FDA group and the Zurich group have suggested that the depletion occurs in the tissues. We've published some results more compatible with depletion in the liver or the kidney tissues.

Dr. Margolin: I thought a function at the endothelial level, the blood cells. That's wrong? The nitric oxide-

Dr. Schechter: What you're thinking of is the fact that pressure on the endothelium or certain hormones like [osteocholine 01:38:01] will increase endothelial nitric oxide synthase NO production. But that's all the NOS production, not the reductive processes. So that gets you back to this dichotomy between those focused on NOS enzymes and those more interested in the reductive. I mean it's like the two ends of the egg. Those who eat the egg from the small end and those who eat the egg from the large end. There are those who believe in the NOS enzymes which are oxidative processes, and those who believe in the reductive processing.

But just to finish this-

Dr. Margolin: ... that's what I was going to ask.

Dr. Schechter: ... is that we, in our own work in our last five years, have shown that the reductive pathway is valid by showing that normal deoxy red blood cells, in the presence of nitrite ions in the plasma, will cause inhibition of platelet aggregation by forming NO from the nitrite, which was predicted by the work we previously did. We did experimental work to confirm this pathway, and we think that the difference between arterial and venous clotting may be effected by this reduction of plasma nitrite by red cells.

More recently we've worked on muscle blood flow and accidentally discovered that normal muscle in rats and mice have very, very high levels of nitrate ions. And this, to our knowledge, nobody ever measured this before. And the nitrate levels are much higher than any other organ. And we think the nitrate in muscle is reduced to nitrite and then to NO with exercise. And so blood flow increases in exercise, which could be tenfold or 50-fold, increases are modulated by nitrate reduction.

Dr. Margolin: I see. Very important aspect in an energy metabolism.

Dr. Schechter: Yes. A group in Europe has confirmed our findings in rodent muscle for human muscle, and we now have permission ourselves to study human muscle. It took a long time to get NIH-

Dr. Margolin: In terms of this hypothesis in sickle cell, are you stating that you feel that most of the vascular problem in sickle cell is on the arterial side?

Dr. Schechter: ... yes. That actually is a very important point. I'm glad you mentioned that because the work that Dr. Noguchi, Rogers, and I did, based upon the idea that the problem in sickle cell disease is arterial, in the precapillary arterials and the [inaudible 01:41:14], not in the capillaries and veins as classically envisioned. And we've had a great deal of trouble communicating this idea which we think is central to understanding the pathophysiology of the disease. And again, the nitric oxide would be irrelevant if that were not true because we want to enlarge the blood vessels and blood flow. You can only do that on the arterial side.

Dr. Margolin: Will this bring you up-to-date on your present research?

Dr. Schechter: Yes.

Dr. Margolin: Then I think we're going to stop here and come back for more comments in another week. But this has been very fascinating. And I tell you, I'm overwhelmed with all the spinoffs that come from what seems like simple direction and research that has changed all our thoughts and thinking of the concepts that you started with.

Dr. Schechter: Thank you.

Dr. Margolin: Fascinating.

Dr. Margolin: It is now March 20, 2018 and Dr. Schechter and I are continuing this endeavor to complete the oral history that we started a week ago. Dr. Schechter, we were talking about the differences in individuals with sickle cell, despite the fact that they have all similar gene problems or issues. And then you were telling me that you had some interest in relating the bench work to your clinical studies and I'm really wondering how that worked out and some of your thoughts about that and about what it meant to NIH to combine those two issues. So I'll let you go on and tell us about your experiences.

Dr. Schechter: Thank you, Gordon. I'm enjoying this interview and I hope people who might look at it will find it of interest.

Dr. Margolin: I guarantee it.

Dr. Schechter: We spent the time last week talking about my research first in protein chemistry and then in sickle cell disease. And as I indicated, in the mid and late 1980s I moved from a primary focus on basic research having to do with hemoglobin and related molecules to some clinical aspects of sickle cell disease. In particular the potential of using agents like hydroxyurea to elevate fetal hemoglobin to improve the symptoms and the manifestations of sickle cell disease.

And so after 30 years of doing basic research I became involved primarily with Griffin Rogers and also individuals from the Heart Institute in clinical studies in the late 1980s. And at that point I was very happy because this, after all, had been my reasons for going to medical school and taking clinical training before I came to NIH. And although I have primarily worked in the laboratory in my first several decades at NIH, the NIH always represented for me a place where [inaudible 01:44:36] you combined basic and clinical research. And we were very fortunate to be able to do that in our clinical studies.

But during this time of getting involved in clinical studies in the late 1980s, I began to realize that it was much more difficult to do clinical studies than even in the intermural program at the clinical center, the National Institute of Health, because many things had changed over the decades. And with each year, doing studies on patients became more and more difficult. This was in part due to the more complex rules, having to deal with institutional review boards and what was allowed and what was not allowed. And also the difficulty and expense of doing clinical studies in general. But I also began to perceive that the powers that be in American medical research, both at NIH and more generally, were not as enthusiastic about academics like myself. And I call myself an academic even though I was working the government. The NIH, as I tried to indicate before, was really very similar in its goals and structure to most academic medical schools and research universities and hospitals.

But I began to sense that the clinical research was not as valued as much as the basic research. And these thoughts, which were fairly inchoate in my part, at the beginning, were crystallized in 1992 when Ed Ahrens of the Rockefeller University published a book called the Crisis in Clinical Research, which reflected five or eight years of his own studies of how NIH intermural and extramural was judging and supporting clinical research. And he had come to the conclusion that what he saw at the Rockefeller University hospital and in general in academic medicine, as well as at NIH, were trends suggesting that NIH was not as interested and supportive of clinical research as it had been from the beginning. From the 1950s, when under Dr. Shannon and others, the focus of the program has always been equally basic and clinical research.

And these thoughts of Dr. Ahrens and others, which were reflected in position statements of a number of professional societies, began to build up during this time and led me and others to publicly question some of the assumptions of how the research program, both intramural and extramural, under the aegis of the NIH, was being administered. And in fact, in 1998 I published a commentary in The Journal of the American Medical Association questioning the NIH commitment to clinical research. And this commentary did not go over so well with some of the leaders of NIH. Although there were many academics who noted that I had done this. Whether it was Dr. Goldstein and Brown or the officers of American Society of Clinical Investigation and several others who were very active in these endeavors, we held many meetings and several programs were started with the Institute of Medicine. And we got professional societies, including FASEB at that time, to try to increase the commitment of NIH to supporting clinical studies in clinical research.

And I should mention that actually some of the concerns go back to 1979 when Dr. James [Weingarten 01:49:01] who's later one of the NIH directors, published an analysis of the percentage of grants going to physicians. And he noted then in 1979 that whereas the numbers of PhD investigators, MD investigators had been about 50-50 in 1965 or 1970. By 1979 there was a preponderance of non-physician investigators. And that trend was continuing, I think, at that point at about 75% PhDs and 25% individuals with medical credentials. And so we and myself and many other groups, tried to impede or slow down this change of the NIH portfolio.

One thing we were amused, I noted in some of my history endeavors, which we'll talk about a little later, that when NIH was first active and created in the 1930s with the Ransdell Act, it was talked about as a medical research agency. Then after 1946 when the CDC split ... I'm sorry. It was originally considered a health research agency, such as the National Institute of Health. But then after 1946 when the CDC split off, more and more of the NIH deemed itself a medical research agency. And then by the 1970s and '80s it began to call itself a biomedical research agency to try to encompass the individuals doing more fundamental biological research. And that was, in a sense, okay, although it indicated that at a level not necessarily conveyed to Congress and the public, the NIH itself pride itself on biological as well as medical research aspects.

However, by the 1990s the then NIH director and others began to call the NIH a basic biomedical research agency, or even a fundamental biomedical research agency. And I and others became concerned that in broadening into the basic fields the NIH was letting down the support of the clinical aspects. And I think this indeed as continued in the last 20 years since my 1998 paper or similar paper from [inaudible 01:51:55] or Lee Rosenburg had printed, or others who were very active in the late '90s and the first decade of the century in trying to broaden the NIH mission and mandate. And unfortunately now the trend has continued so much that it's very difficult to get support for truly clinical studies either in the study sections that [inaudible 01:52:25] to fund its grants, or within the intermural program, in which the clinical aspects have continued to shrink here at the clinical center.

Dr. Margolin: I think what you're saying is also reflected in many of our medical schools in the country where the basic scientists are almost all PhDs now, whereas at one time they were MDs. And where they're beginning to recognize that the PhDs don't always reflect the clinical needs of the medical students. And we're seeing right now a great upheaval in trying to redirect the basic scientists into more clinically oriented areas. And perhaps this is the revolution you have been waiting for, that you're describing.

Dr. Schechter: I'm hoping that. I mean one of the consequences of the trend that began perhaps in the 1980s or certainly by the 1990s was that more and more important clinical studies have moved to Europe. That, for example, the number of cooperative oncology groups have shrunk, and the number of studies they fund have decreased. There was a recent science report mentioned in a study done in Baltimore, which noted that the clinical studies funded by NIH has shrunk in the last five years by 39% from some like 800 or 850 to 400.

Dr. Margolin: That's in the last five years?

Dr. Schechter: In the last five years. So the trend is continuing. The movement of important clinical work is going more and more abroad. And I don't think in terms of the benefits to the public this is a good thing where more and more of clinical work is not only maybe done abroad, but it is only funded by the pharmaceutical industry. And there were many important studies in the past that could be done now, funded by academia, including the NIH. I should mention that the last several NIH directors have pushed back against this trend. Dr. Elias Zerhouni, who I think was one of the very, very good NIH directors, although that was not fully appreciated when he was here for a variety of reasons. Now Dr. Francis Collins have both started programs. In Dr. Zerhouni's case it was called the Roadmap. In Dr. Collins' case it's called the ... There's a fund name I'm blocking out right now. I'm sorry, the fund is called the Common Fund, of Dr. Collins, are being used to either start new institutes and new programs like NCATS or finding specific clinical programs such as the All of Us program, more recently to correlate genomics with health. But there's been tremendous resistance on the part of organizations like FASEB and academics who believe that only R01 grants are the coin of the realm, and that large clinical projects, either intramural or extramural, are in conflict with the R01 mechanism.

And so these are only part of the issues. The issues also relate to the expense of doing clinical work. The difficulties that ethicists bring to approving clinical studies, and other aspects. But that effect is that during the more than half century that I've been trying to do research, I've noticed that the public contribution to clinical studies and clinical questions, which could have a large impact on public health and the like, has shrunk greatly as compared to when I first trained.

Dr. Margolin: Those are very interesting observations. But in your own particular experience, did you get into the clinical enough to be able to really get your feet dipped into the water?

Dr. Schechter: Yes. I mean I think I was fortunate starting in 1985 to be a co-investigator over the last 30 years or so between 10 and 20 clinical protocols. Although I never had direct responsibility for patient care, I was involved in planning the studies and getting the studies through the institutional review boards and collecting the data and helping write the papers, which appeared in the New England Journal of Medicine and other very important journals. And I think they made some contribution to the fields we discussed last week. But certainly I did not have the experience that individuals who do the clinical research full time have. Although in discussions with them, I sensed their frustration about many aspects of the system right now.

Dr. Margolin: And you believe the word translational that's been thrown around a lot the last few years, has come out of all of this and may make a difference?

Dr. Schechter: Yes, I'm glad you raised that point because I had meant to comment on that. I think it's very interesting. As far as I know, the term translational science, that it's unusual etymology having to do with changing from one language to another, was first used in an application to medical research in the 1990s. It's not a very old term. And my understanding, and I'd like to pose this if anybody can correct me on this, is that the term was introduced in a strong way to medical research by Dr. Elias Zerhouni when he was planning what became the so-called CTSAs, or clinical translation ... The Clinical Science and Translational Award, CSTAs, to replace the old GCRCs, the old General Clinical Research Centers that had been funded for 40 or 50 years by NIH. And Dr. Zerhouni envisioned a much bigger program which he thought would be as important to medical centers as comprehensive cancer centers. And I'm not sure they've achieved that goal. But Dr. Zerhouni believed to broaden the mandate and to improve the funding and importance of clinical research.

Unfortunately, this did not come to pass fully because in large part the NIH budget, after a period of rapid growth, was frozen just as these changes were being made. But interestingly, my understanding is that Dr. Zerhouni added the term translational to these awards in order to make basic scientists feel welcome to the program, whereas they had been largely excluded from the GCRC program, they now could have a place in these new reconstituted clinical units in individual medical centers. And although there will be fewer, there may be 50 compared to the 80 or 90 with the GCRCs, the CTSAs, I think the Clinical and Translational Science Awards, I think that is the correct name, I may have misspoken before, would have a larger inclusive aspect. And I think that the main achievement, the choice of adding the term translational to those awards, was that everybody in the U.S. at least, realized that they had to include the term translational in their grant applications and the like. And so it became very commonly used, although I think the meaning was never really clearly defined or understood. And I'm not sure, in retrospect, that it advanced the situation beyond calling some things basic and some things clinical. But it became a way to attempt to meld basic and clinical research, not necessarily to the advantage of the clinical investigator.

Dr. Margolin: It's interesting to me, go back to one of your earlier comments in this discussion when the bench people, namely you, were interested in the clinical observations that the first six months of the child's life there were still fetal hemoglobin, and which you were able to translate back to your research bench. And now we're talking about going from the research to the clinical. And it seems to me it's a two-way street no matter how you look at it, if we really deal with it in the global sense.

Dr. Schechter: Again, thank you for making that point because I think it relates to another fundamental issue that I've been concerned with for 20 or 30 years, and that is the relationship between basic and applied research. The assumption has been that basic research leads to applied outcomes such as clinical applications. And there have been groups that have met and issued reports on this, including a group [inaudible 02:02:28] medicine, which I was [inaudible 02:02:31] as an observer, which I actually formulated two or three steps in this linear translation for basic to applications in medicine. But I think that this concept is fundamentally incorrect. That I think that the clinical research, as often of more, leads to basic advances. And as you said, there is a two-way street. And to assume that basic research is the underpinning of clinical research is simplistic and only tells half the story. And I think that there have been books and papers written pointing out the complexity. Dividing the research into four quadrants, for example, or showing of how the clinical observations, and the case you gave in sickle cell disease is a case in point. That with Janet Watson at Downstate Medical School, observation about the delayed severity of sickle cell disease which led to the identification, the realization, the importance of fetal hemoglobin, which now underpins most of the major advances in the treatment of the disease 50 years later.

In fact, as I mentioned to you earlier, last Friday I was at a small workshop at the Heart Institute just discussing how to approach increasing fetal hemoglobin in sickle cell patients. And so with clinical observations that led to years and years of basic study, and hopefully the basic study will go back into the clinic, but if you cut out one you markedly weaken the other in either case. I've sometimes thought that an ideal NIH portfolio would be one-third truly basic research, one-third truly clinical research, and one-third so-called translational research, which is a little blurry and covers the relationship between the two. But we've gone far from this one-third, one-third, one-third null position to where the clinical aspect may actually only be five or 10% of the enterprise. Although the institution claims that it's much higher.

Dr. Margolin: While we're back to sickle cell now, and clinical, what is your thoughts about the potential for truly curing sickle cell disease and being able to truly modify the disease other than by this manipulation kind of thing that you've been doing?

Dr. Schechter: Well this question, in many ways, underlies the meeting that I was at last Friday. And I believe there's another meeting going on today and yesterday in the sickle cell community about the ultimate goals. At the one hand the NIH would like to use the advances in gene therapy and related bone marrow transplantation as a way to continue the development of truly curative therapies, either by stem cell or bone marrow transplantation or by gene therapy. Especially with the CRISPR/Cas advances of the last several years.

The problem with that is that this will be and is extraordinarily expensive and difficult and still very risky. And so even if these techniques are advanced greatly and become easily done in the next five or 10 years, and I doubt it will be any sooner than that, undoubtedly, they will be expensive beyond any reasonable belief and not applicable to a great many individuals. And so the meeting last Friday was to concentrate on small molecules, hopefully that could be made cheaply and sold cheaply, although whether that would happen is uncertain. That could be more widely used both in this country and in the world.

So I think probably with the advances in gene therapy, that truly curative approaches will emerge in the next decade or two. But whether or not the current system of pricing medical treatments that'll be applicable to more than a small number of individuals is really not clear.

Dr. Margolin: I'm thinking about a spinoff of cure of one disease, which made it enhance development in another. It seemed to me I remember that it was determined that the individual with sickle cell were protected from ...

Dr. Schechter: Malaria.

Dr. Margolin: Malaria. And now if you cure sickle cell will the malaria get worse?

Dr. Schechter: It's the individual with sickle trait not sickle cell who's protected from malaria. To some extent, not fully. But to some extent. So in this country that's obviously not an issue because malaria's virtually non-existent. Whether in Africa, if you did get a small-

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Are virtually non-existent, whether in Africa, if you did give a small molecule wet, it would worsen that aspect. It's something to be concerned about.

Dr. Margolin: It a consideration, yes. It really is interesting when you play that game with all of medicine. We have people living longer, and now they have more problems as older ...

Dr. Schechter: Yes, unintended consequences.

Dr. Margolin: Exactly. [crosstalk 02:08:25]

Dr. Schechter: Results could easily emerge from the [inaudible 02:08:29].

Dr. Margolin: So any decisions have to be made carefully and thoughtfully, obviously.

Dr. Schechter: Yes, sir.

Dr. Margolin: Let's leave the sickle cell and the research now. Let's get to some of your other involvements in areas of medical education, and setting standards for behavior in medical and scientific rules and others of your multiple program activities.

Would you like to speak first about your interest in your relationship to the FAES?

Dr. Schechter: Okay. Well, let's start with the history program which I think...

Dr. Margolin: Oh, alright. You want to do that first.

Dr. Schechter: I think that more closely relates.

Dr. Margolin: It has to do with the history of the Office of NIH History and the Stetten Museum, right? Yeah, go ahead because we represent that and this oral history will be deposited in that department.

Dr. Schechter: Right.

Dr. Margolin: So let's hear it.

Dr. Schechter: Thank you. So I was thinking of what to say about that, and in that case I wanted to honor DeWitt Stetten or Hans Stetten who was the one founding scientific directives, what became my institute now, NIDDK, later was the founding dean of Rutgers Medical School, and came back to NIH, first to head the National Institute of General Medical Sciences, and then become deputy director of the Intramural NIH for Research, which he did for many years.

He was also a prominent textbook writer, a physician trained at Columbia University, but Dr. Stetten had to retire from his physician as deputy director for Intramural Research because of his failing vision. He had macular degeneration. I believe that that was the syndrome.

He was given an office in the Stonehouse after he retired as deputy director, and during those years, I think in the early 1970s, he wrote an autobiographical essay or book, which I think is available in the NIH History Office website. In addition, he conceived the idea of having a formal history program at NIH. The NIH like other government agencies had somebody like a historian who was in charge of referring records to the archives. Not somebody who ordinarily did more academic history.

Dr. Stetten began to get a group of half a dozen individuals from around the NIH campus to meet with him once a month at the Stonehouse, and I, fortunately, for reasons I never fully understood was one of those individuals. During those meetings, I think in 1973 and 1974, we formulated the idea of having a formal academic type history program at NIH.

Dr. Stetten sent a memo to Dr. Wyngaarden who was then the NIH Director and who also had been Dr. Stetten's mentor ... I'm sorry, Dr. Wyngaarden had been mentored by Dr. Stetten when he was a clinical associate here at NIH. Dr. Wyngaarden approved the memo, and created a History Office, which was assigned to the deputy director of NIH Communications, which was not necessarily the best location, but for a variety of reasons, that was the easiest bureaucratically to organize the program.

The History Office was created by Dr. Wyngaarden as NIH director, and fortunately, Dr. Victoria Harden, who had written and published a book of the first 50 years of NIH history, was doing a post-doctoral fellowship in the history of medicine at Johns Hopkins, and she was recruited to come to NIH to be the first official historian, and became the Director of the Office of History.

After Dr. Stetten's death, another ... I should say even before, initially the History Office had two components. It had a component for doing academic history of the type we're having now with this oral history discussion, also collecting instruments and other so-called artifacts from NIH's history that might be preserved and displayed either in a [inaudible 02:13:26] museum, or around the campus. Some of the people who met regularly with Dr. Stetten were interested in collecting the instruments and some like myself were more interested in the more academic aspect.

So both were combined, so became the Office of NIH History, and the museum of collections after Dr. Stetten's death, the museum aspect was renamed the Stetten Museum, and the other is still, I believe, the Office of NIH History. From 1975, I think when Dr. Harden was named the director of both programs to her retirement in 2005, she ran the program and I think did a superb job in both aspects. There was in the beginning an advisory committee to both programs, which met twice a year, and I was from the beginning on the advisory committee about 10 years. From 1990 to 2000, I chaired the advisory committee.

That led to those programs led to the first oral histories as well as much else. I'm sure that'll be a separate topic. During the period after Dr. Harden's retirement in 2005 largely because of the ill health of her husband, there was a delay before a search was initiated for a new historian, and I became the acting NIH historian for two years from 2005 to 2007 just in order to keep the programs going. Although when the position was finally announced, and people were encouraged to apply to be the historian, I did not choose to apply for a variety of reasons, including that my own research had been going very well at that point, and I did not want to give up my primary research program.

Also, and I say this honestly, I also became concerned during the two years that I was the acting historian about how deep the support for history programs were at NIH. There was a period when the budget was no longer growing, and I heard a lot of complaints about the rather limited dollars we were spending in the history program that should be used for research per se. I became aware that both because of the organizational aspects of the History Office and the competition with other programs for funds, that being the historian would require continuous fighting for resources.

I think my concerns were born out years later after the historian who was recruited in 2007 retired and it was decided not to fill that position any longer, and the History Office, which Dr. Harden had created and very good quality, and has some very excellent employees still working have not had a true leader now for five years or more because the NIH has not necessarily wanted to commit to that position or the deputy position and the like, which I think is very unfortunate.

Anything this interview conveys is the need for revitalizing the history program, and identifying historians and more people because I think in the long run the future of NIH itself depends upon understanding the past and seeing the future in those terms. But that has been an issue in recent years.

I should still just to complete this aspect of it, and maybe we can go FAES now, even since 2007 and the last ten or eleven years, I had an informal title of Senior Consultant to the History Office. I have been active in helping them organize several meetings. I've tried to mentor some of the staff members. I've read papers from post-doctoral fellows, and I think I've done what I could to try to bolster the continuation of the program. I'm on several advisory committees related to the History program, although it's clearly a back burner in the total NIH portfolio right now.

Dr. Margolin: Well, we thank you for all your efforts in this regard because obviously I'm sitting here representing that segment of NIH, and I think it's really important and they've got an awful lot of material there that needs to be dealt with and enhanced and to be better known on the campus.

Dr. Schechter: I agree with you fully, and I appreciate your efforts and those of the former employees as well as other volunteers who come during the years.

Dr. Margolin: Well, it's a struggle for the office.

Dr. Schechter: Right.

Dr. Margolin: Alright. Now let's hear a little bit about FAES? Your role.

Dr. Schechter: Okay, and I would say that in many ways that parallels my interest in role in the History Office because the FAES, the Foundation for Advanced Education in the Sciences, Incorporated was incorporated in 1959 as an Educational Foundation in the State of Maryland organized by I believe 11 senior NIH scientists, including Dr. Seymour Kety and my mentor, Christian Anfinsen, as well.

It came from the scientists, not the administrators, and the background was in the early 1950s after the clinical center opened, and after the NIH began to expand under Dr. Shannon, individuals realized that one needed educational activities for the staff, for the scientists and the physicians as well as technicians and post-doctoral fellows and the like.

We were very far from the nearest universities and even the nearest universities did not have very much in the way of state-of-the-art studies related to the kind of things we'd done for research at NIH. The initial response was to contract with the Department of Agriculture, which had its own evening school since 1919. I believe during the first World War, the Department of Agriculture realized that it needed its own staff to be able to train them in modern aspects of product development and other agricultural sciences, which is a very farsighted, endeavor. That school initially connected with the Department of Agriculture still exists. I think it's now called the Graduate School, but it's independent of the Department of Agriculture right now. But it still exists and gives courses. So about for about five or seven years, the Department of Agriculture night school gave ... individuals supported by them, gave courses on the NIH campus for the scientists. But many of the scientists realized that agricultural science and medical sciences had split many years ago, and this was not an ideal pairing.

So by 1959, the more academic scientists like Doctors Kety and Anfinsen that I mentioned decided that the scientists themselves would teach courses and we had to be able to organize it ... the courses ourselves. So they created with Dr. Shannon's blessing an organization called the FAES or the Foundation for Advanced Education in the Sciences and a one-page authorization memo with Dr. Shannon was worked out. For the next 30 or 40 years that one-page memo covered the relationship of FAES, which was a private organization having the ability to contract with NIH for offering courses.

Later on a bookstore and then a weekend afternoon concert series was created by Dr. Cantoni, which lasted for 40 years, I believe. A graduate program with Johns Hopkins was created, and ultimately even some quasi business enterprises like the expanded bookstore and a health insurance program for non-federal employees who are here at NIH as post-doctoral fellows.

The FAES has flourished since 1959. I joined the Board of Directors in 1972 or 73, and have been almost continuously on the Board of Directors and is served various years, president and the other executive officers and I've gone off the Board several times because of term limits in the Bylaws, but currently I'm secretary of the Executive Committee of the foundation, and I think the program just in a few sentence summary attempts to make the NIH more like a university than it would, otherwise, be in contrast to many government agencies in which the university aspects are minimized. I think this relates to the large numbers of post doctoral fellows and the turnover of these fellows and their need for education or the need even for practice in teaching, which we try to encourage.

So one of the reasons the Intramural program has been so strong in the last 60 years is because of the existence of the FAES, and I devoted a fair amount of my own time to its administration. I chaired the combined graduate program with Johns Hopkins for a decade, and related to that, I gave lectures in some of the Johns Hopkins courses for 15 or 20 years.

So I think that it began like the history program ... this was the aspect of the intellectual excitement around the NIH campus, which I think has been very important to keep it at the forefront of medical research.

Dr. Margolin: As a side issue, when I look at the table of contents of the offerings of FAES is, they're really basic research oriented, which fits into your concept of what NIH has been doing or what the whole medical world has been doing. Am I right?

Dr. Schechter: Yes. I mean that again is an issue that early on, for example, we had lots of board review courses or even some courses that were devoted to more clinical topics, and those have been difficult to maintain. I think that, again, the vast majority of courses are very basic. Again, the balance that existed at NIH from its present incarnation in the late 40's, early 50's, which I think is when the NIH as we know it really crystallized, has slowly dissipated and not for the better.

Dr. Margolin: I think maybe a spinoff of some of that. You got involved with what was called the NIH director's committee on conduct of science and ethics and the AAES Committee on Scientific Freedom and Responsibility and you've written some ... co-authored some very important papers in that regard. Would you speak to those items because it's all part of this whole educational issue as I see it.

Dr. Schechter: Yes. In part my involvement in those several aspects probably relates indirectly to the two things we've just been talking about, the History Office and the FAES. In that in my role in these organizations, I got to know many individuals who later became senior administrators, institute directors or deputy directors of Intramural Research like Dr. Wall and Dr. Stetten or had other important administrative posts.

There's one thing that I think for a junior scientist to be in such committees, which I think is a strength of medical schools, which doesn't follow here at NIH where the people try to minimize committee involvement. It gets one to know what senior people and get comfortable with them. For example, when NIH ... the Intramural program realized it should have guidelines for the conduct of research. In the 1980s there were several very well-publicized cases in which research seemed to have been done fraudulently, the case at Memorial Sloane Kettering of the painted mice or allegations, which largely were untrue, you had South Baltimore, there was realization that institutions should have some formal guidelines, and Dr. Wall who was then the deputy director for Intramural Research, I knew well from the FAES, and he asked me to be on a committee about a dozen institutes to write the guidelines for the conduct to research.

We had several meetings to discuss what should be included, and for reasons that I don't remember, I got the task of writing the first draft of these guidelines, and over a period of a couple of weeks I produced the first draft, which was then distributed to the committee and we refined them. Eventually a booklet was published under Dr. Wall's egress called Guidelines for the Conduct of Research at the National Institute of Health. That document is now in the 5th or 6th edition published by Dr. Gottesman, the current deputy director for Intramural Research, but has been updated several times.

Later on because of my experience with that, I was asked to be on a committee on mentoring, and again, I was given the task of writing the guidelines, which I did on an airplane flight from London to Washington. That I find is the best place for writing such things, and my Guidelines for Mentoring was tweaked by the committee and was again published as the official NIH guidelines.

But these enterprises led me ... when the NIH Director decided there should be a committee on Conduct of Research led me to be one of the first appointees to that, and I served for five or six years on that committee. Also, through contacts outside of NIH on various committees or without in part due to my activities about improving clinical research, when the American Association for the Advancement of Science wanted to fill its formal committee that's existed already since 1950 also related to conduct in research, somebody recommended me. I'm not sure I would be allowed to do that these days because of some of the critical rules about federal employees, but for six years I think I was in two/three terms on the American Association for the Advancement of Science, a very well-known, prestigious committee on scientific conduct. Again, we looked at individual cases of allegations related to that as well as questions about the treatment of scientists in many communist and Latin American countries.

So, again, all this sort of interactions of the history program, the FAES, the conduct of science committees are all, unfortunately, largely it's the same people who participated in any of these activities. A lot of scientists, for example, just are uninterested in such endeavors. I think one of the reasons I feel, and still to come to work each morning, not only is the research, but there these other activities, which I think have a lasting influence on the nature of research, which I'm still fortunately involved in.

This segues perhaps into the last Assembly of Scientists.

Dr. Margolin: Okay.

Dr. Schechter: Which again is probably not completely independent of these other three programs we've talked about, but again in 1959, the same year that the FAES was created, the scientists in what was then the National Institute of Mental Health and the National Institute of Neurological Diseases, which at that point were administered as one intramural program, created an Assembly of Scientists modeled after a university academic senate, and they recently published a short history of this program in the NIH Catalyst, the March/April issue.

They created this Assembly of Scientists not only to deal with administrative aspects, but also to have input to the leaders of NIH about science policy and the like. One goes back to the VDI [inaudible 02:34:04], it's clear that this endeavor was welcomed by the leaders of NIH, and I think that again was unusual for a government research agency, but did reflect the fact that in the 50s the NIH was recruiting a lot of academics who were used to having such academic senates and the like. The Assembly of Scientists, which was created [inaudible 02:34:31] gradually spread so virtually to every institute and there were probably about 10 institutes at NIH in the 1960s. Now there are 25. It had its own Assembly of Scientists and there was an Inter-Institute Council, which tried to harmonize the activities being the original assemblies.

But the real test of these groups was the push against the Vietnam War, which started in 1965 and 1966 when most NIH scientists objected strongly to our involvement in Vietnam, and wanted to have demonstrations or even lectures by people like Dr. Benjamin Spock, who were articulate opponents of the war with Vietnam. So the Assembly of Scientists became the coordinator for federal opposition at NIH to the war in Vietnam, and those were interesting times in their own rights. But after 1975, there were some also concern with President Nixon's firing of several NIH directors because of a feeling in the White House that they were not loyal enough to the President. This included Dr. Stone and Dr. Marston who were all fired by the Nixon White House because of the feeling that they did not have sufficient loyalty to the White House. The Assembly of Scientists held meetings and protested these events, which were highlighted in the New York Times and the Washington Post among other places.

But for 30 years these assemblies became relatively inactive until 2005 when new, fairly draconian ethics rules were [inaudible 02:36:29] for NIH scientists, which would've endangered the professional responsibilities and of duties of NIH scientists, The involvement with professional organizations, sponsored travel, accepting awards, being able to be an officer of a professional society, even an editor of a professional journal would all go into question.

The Assembly of Scientists was reconstituted and I had been an officer of the assembly back in the 60s and 70s, and again since 2005 when the Assembly of Scientists was reconstituted, I've been fortunate to be on the Executive Committee of this group and have tried to coordinate the pushback, which I think has ameliorated some of the worst aspects of the proposed rules.

So again, ironically, many of the same people appear in all of these different guises, and I'm not sure that in the long run that's a good thing, but that's how things tend to be.

Dr. Margolin: Well, we're talking about history here. You certainly represent the history of this whole organization in many aspects, the scientific, and the nonscientific educational relationship to patients and all that. It strikes me terribly important, and I'm really overwhelmed to hear you and to realize that we've just barely scratched the surface on your major other endeavors. For example, you've been co-editor of the Perspectives in Biology and Medicine for ten or more years. You've done scientific review committees for NIH and the Food and Drug Administration, the National Science Foundation and the Howard Hughes Medical Institute, and you've been teaching as a faculty member at Johns Hopkins, and George Washington University School of Medicine.

I can't imagine a busier life, and yet you still produce way over 300 medical articles, and influence a great deal of thinking in the whole medical world. It is such a pleasure to know you and to talk to you, and I wish we could go on for hours and hours, but nobody's gonna read very much more of this oral report if we keep going. So I'm gonna have to bring it to an end and thank you for your service, and your fantastic, fantastic scientific accomplishments and your willingness to spend this time to relate it, and I do think this will go into the archives that we've got, and will obviously represent a very important contribution to the Office of Medical History and the Stetten Museum. I'm very grateful to you for your time and effort.

Dr. Schechter: Thank you.

Dr. Margolin: Thank you.

PART 5 OF 5 ENDS [02:39:23]